*Polymer Science, Ser. C, Vol. 42, No. 2, 2000, pp. 208–228. Translated from Vysokomolekulyarnye Soedineniya, Ser. C, Vol. 42, No. 12, 2000, pp. 2328–2352.*
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# Responsive Polymer Gels[1]

**O. E. Philippova**

*Department of Physics, Moscow State University, Vorob'evy gory, Moscow, 119899 Russia*

Received March 22, 2000;
Revised Manuscript Received April 19, 2000

**Abstract**—Experimental data on the fundamental properties of polymer gels—ability to undergo superstrong swelling and collapse—are reviewed. The main types of "responsive" gels are presented and the main possible applications of these systems are considered.

## INTRODUCTION

Polymer gels are three-dimensional crosslinked polymers swollen in a solvent. These systems can be of both natural (e.g., vitreous body of the eye) and synthetic (polyacrylamide and poly(acrylic acid) gels) origin.

The content of solvent in a gel may be very high, reaching up to 99.9%. Despite the fact that polymer gels consist predominantly of water, these objects are capable of retaining their shape like solids. This property is due to the polymer chains being crosslinked so as to form a common spatial skeleton called the polymer network. The crosslinks between polymer chains can be provided both by labile entanglements formed by weak bonds (e.g., by micelles, multiplets, crystallites, etc.) and by stable covalent bonds (Fig. 1.). The polymer gels with crosslinks of the first kind are referred to as physical gels, while those crosslinked by covalent bonds are called chemical gels. In this review, consideration is restricted to the gels based on covalently crosslinked polymer networks.

The first chemical gels studied were based on polymer networks with a high density of crosslinks, which exhibited very small swelling in solvents. These gels are widely used in many fields, in particular, as carrier media in chromatography. In recent decades, the attention of researchers was drawn to the so-called slightly crosslinked gels, with the density of crosslinks on the order of one per 50–400 polymer chain units. These systems are capable of absorbing and retaining very large amounts of a solvent, the mass of solvent being greater by several orders of magnitude than that of the polymer involved in the gel network. In other words, these gels possess superabsorbent properties or are capable of superstrong swelling. Another characteristic property of slightly crosslinked gels is their ability to undergo collapse, where the gel volume drops by a factor of several tens or hundreds in response to small changes in the external conditions (temperature, pH, etc.). Both characteristic features of the slightly crosslinked gels (superstrong swelling and collapse) are most pronounced in polyelectrolyte gels containing ionogenic groups capable of dissociating with the formation of charged units and counterions (Fig. 2) [1, 2].

What physical laws stand behind these properties of slightly crosslinked gels? The ability to undergo strong swelling is related primarily to the effective repulsion between polymer network units in the gel. The repulsion is most frequently caused by the "exerting" osmotic pressure of mobile counterions contained in the gel. The collapse is possible if attractive forces, capable of effectively counteracting the "exerting" osmotic pressure, are also operative between the gel network units. The collapse takes place when an external factor (temperature, pH, etc.) stimulates the growth of attraction between units, which results in the absorbed solvent being abruptly released from the gel. Owing to this behavior, slightly crosslinked polymer gels are frequently called responsive gels [3]. This term means the ability of a gel to respond to external factors capable of inducing the collapse.

The aforementioned competition between attractive and repulsive forces can both modify the gel state on a macroscopic level (swelling or collapse) and produce

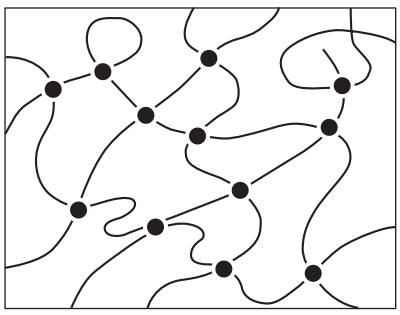

**Fig. 1.** Schematic diagram of a polymer gel. Black circles indicate crosslinks between polymer chains.

[1] The work was supported by the Russian Foundation for Basic Research, project no. 99-03-33447a.

microscopic changes manifested by the formation of regular microstructures on a 1–100 nm scale [2]. The latter microstructures also exhibit a "responsive" character and can be controlled by external factors.

In order to control the properties of polymer gels on both macroscopic and microscopic levels, it is necessary to study the fundamental laws governing the behavior of these systems. Below we will consider the principal factors determining this behavior and discuss their role in manifestations of the properties of responsive polymer gels.

## FACTORS DETERMINING THE BEHAVIOR OF POLYMER GELS

### *Uncharged Gels*

The behavior of a gel containing no ionogenic groups is determined by non-Coulomb interactions. These include van der Waals forces, hydrophobic contacts, and hydrogen bonds.

**Van der Waals forces.** These forces determine the interaction between dipole moments induced in initially uncharged atoms or molecules approaching one another. The energy of these interactions is rather small, being on the order of 4 kJ/mol [4, 5] (cf. room-temperature $kT \sim 2.5$ kJ/mol).

The mutual attraction due to the van der Waals forces between uncharged network units in a gel can be enhanced by adding a thermodynamically poor solvent to the system. As a result, the gel shrinks as a whole. An example is offered by the contraction of a water-swollen polyacrylamide gel upon adding acetone [6, 7]. However, it is not excluded that a certain role in stabilization of the compact gel configurations in this system belongs to hydrogen bonds between acrylamide units.

**Hydrogen bonds.** A hydrogen atom covalently bound to an electronegative atom A (e.g., O or N) has a deficit of electron density that can be compensated by shifting the H atom toward another electronegative atom B possessing an unshared electron pair. As a result, the H atom forms a hydrogen bond between atoms A and B (A–H···B) with an energy of 12–38 kJ/mol [8].

Single hydrogen bonds usually cannot modify the gel state to a significant extent. The role of hydrogen bonds markedly increases if these contacts acquire a cooperative character, as, for example, is the case of hydrogen bonds between the units of two complementary macromolecules. These intermacromolecular reactions may take place between crosslinked and linear polymers (e.g., in a PMAA gel–linear PEG system [9–19]) or between two crosslinked polymers (e.g., in interpenetrating networks of poly(acrylic acid) with polyacrylamide [6, 20–22] and with polyethylene oxide [23]).

**Hydrophobic contacts.** The energy of hydrophobic interactions is on the order of several kJ/mol, which is comparable with or somewhat lower than the energy of hydrogen bonds.

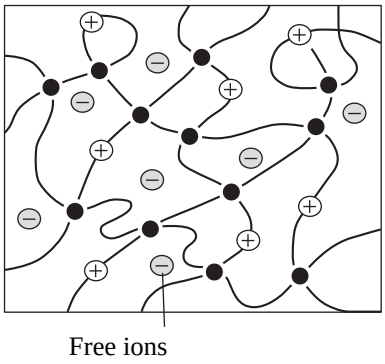


**Fig. 2.** Schematic diagram of a polyelectrolyte gel containing positively charged chain segments and low-molecular-weight negative counterions free to travel over the entire gel volume.

In contrast to the interactions of other types, hydrophobic interactions are closely related to the structure of water as a solvent. When a hydrophobic substance is brought in contact with an aqueous medium, the thermodynamic parameters exhibit a change such that $\Delta S < 0$, $\Delta H < 0$, and $\Delta F > 0$ [4]. In other words, the low solubility of hydrophobic substances in water is a consequence of large decrease in the entropy of the system. This experimental fact is explained within the framework of the following model. Water molecules in the liquid phase are known [5, 24] to form a system with hydrogen bonds, whereby each molecule has four nearest neighboring water molecules. On coming into water, hydrophobic molecules induce enhanced structurization of water in their surroundings, which is related to an increase in the electric potential resulting from a decrease in the local dielectric permittivity around the hydrophobic group. This structurization is unfavorable from the standpoint of entropy. In order to decrease the area of contact with water, the molecules of hydrophobic substances tend to combine with one another. The greater the area of contact between separate hydrophobic molecular groups and water, the more pronounced is this trend.

Thus, the main driving force of hydrophobic interactions is the gain in entropy achieved by decreasing the structurization of water in the environment of the hydrophobic groups. Since the entropy contribution to the total free energy of a system increases with temperature, the role of hydrophobic contacts grows with temperature as well.

The hydrophobic interactions in a polymer gel can be controlled by varying the ratio of hydrophilic and hydrophobic groups in the system. The hydrophobic properties of macromolecules can be enhanced, in particular, by introducing hydrophobic substituents (e.g., *n*-alkyl groups) into their side chains. The longer the *n*-alkyl chain, the more pronounced are the hydrophobic properties. As is known [25], *n*-alkyl chain transfer

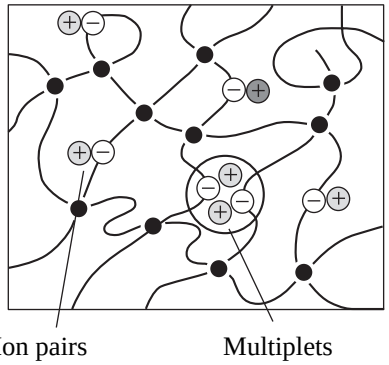


**Fig. 3.** Schematic diagram of an ionomer gel.

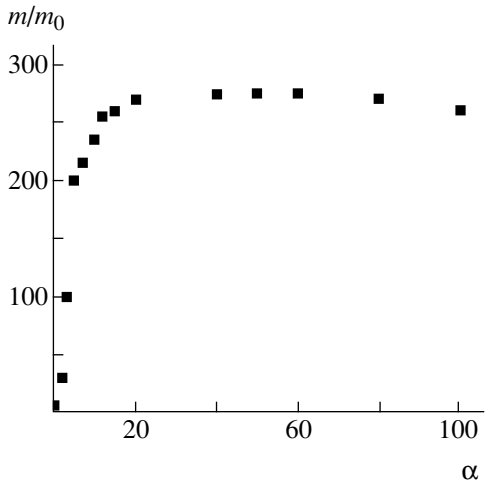


**Fig. 4.** A plot of the degree of gel swelling $m/m_0$ vs. the degree of ionization α for a poly(acrylic acid) gel (1 crosslink per 150 units) in water at 25°C [36] ($m/m_0$ is the swollen to dry gel weight ratio; α is the percentage of charged units in the polymer chain).

from an aqueous to a hydrocarbon medium leads to a free energy gain of $1.29kT$ per $CH_2$ group.

### *Ion-Containing Gels*

An important part in the behavior of gels containing ionogenic groups belongs to electrostatic interactions. These interactions play a determining role in strongly charged polymer gels. In weakly charged gels, where most of the monomer units are uncharged, a considerable contribution to the free energy of the system may be due to non-Coulomb interactions.

In analysis of the electrostatic interactions, we may separately consider several factors, including the translational energy of counterions, the Coulomb interactions between charged groups, and the formation of ion pairs and multiplets.

**Translational entropy of counterions.** When a polyelectrolyte gel is placed into a medium with high dielectric permittivity (e.g., water), the ionogenic groups undergo dissociation with the formation of charged units and counterions (Fig. 2). The counterions may travel over the entire gel volume, that is, acquire a translational entropy. From the standpoint of a gain in the translational entropy, the counterions must tend to occupy the maximum possible volume (without leaving the gel to obey the electroneutrality condition). As a result, the counterions remain in the gel, creating an exerting osmotic pressure responsible for gel swelling [26].

The translational entropy of counterions, determining the osmotic pressure in a gel, is one of the most important characteristics of the polyelectrolyte gels.

**Coulomb interactions.** It must be pointed out that the polyelectrolyte gels are macroscopically electroneutral systems, in which the number of charged monomer units is equal to that of counterions. These systems should be described by taking into account the Coulomb interactions between charges of all types.

In weakly charged polyelectrolyte gels, the role of Coulomb interactions is not as significant as that of the translational entropy of counterions [27]. On the contrary, in strongly charged polymer gels, Coulomb interactions play a determining role and may impart additional electrostatic rigidity to the polymer chain and give rise to the effect of counterion condensation near the strongly charged chain [28–30].

**Ion pairs and multiplets.** In weakly charged polymer gels in low-polarity media, the counterions are not free but form ion pairs with the corresponding charged groups of the network chains [31, 32]. Once formed, these ion pairs may significantly the affect behavior of the polymer gel. The significant effect of even a small number of ion pairs is related to their strong dipole–dipole attraction (with a characteristic energy $E \sim 10–25\ kT$ depending on the pair type and the dielectric properties of the medium) [1]. These interactions lead to the aggregation of ion pairs into multiplets [33] acting as additional crosslinks in the gel (Fig. 3).

## GEL SWELLING

An illustrative example of the osmotic pressure exerted by the mobile counterions is offered by the phenomenon of superstrong swelling of polyelectrolyte gels in water, where the amount of absorbed water may reach several kilograms per gram of dry polymer. The important role of counterions in the swelling of polyelectrolyte gels was established long ago. At the beginning of the 1950s, Katchalsky *et al.* [34, 35] showed that polyelectrolyte gel swelling is determined by the balance between the elastic energy of polymer chains and the osmotic pressure of counterions. Figure 4 shows a typical plot of the degree of gel swelling versus the degree of ionization [36]. As is seen, an increase in

the content of charged units leads to a growth in the degree of swelling by two orders of magnitude. Note that the main effect is observed in the region with a small content of charged units (~10%), where the contribution due to the Coulomb repulsion between these units is not significant because they are far apart. The main contribution to the swelling of these weakly charged polymer gels is due to the osmotic pressure of counterions. This conclusion is consistent with the results of theoretical calculations [27].

Owing to their ability to undergo superstrong swelling, polyelectrolyte gels can be used as superabsorbents for water. Superabsorbent hydrogels are usually defined [37] as hydrogels capable of acquiring a water content above 95%, which implies that the amount of solvent absorbed by a dry gel swollen in water is 20 times the initial polymer weight.

The absorption properties of the polymer gels depend not only on the degree of ionization (determining the osmotic pressure of counterions), but also on the degree of crosslinking and the affinity of a given polymer for the solvent [38, 39]. The superabsorbents for water are usually based on highly hydrophilic macromolecules. Most of the commercial superabsorbents are based on salts of polyacrylic and polymethacrylic acids and polyacrylamide derivatives.

The superabsorbents should not only absorb a considerable amount of solvent, but effectively retain this solvent in the swollen gel as well. For this purpose, the superabsorbent gels must possess sufficiently good mechanical characteristics (strength and elasticity). However, an increase in the water content in the gel usually leads to a decrease in their strength [38]. Thus, creation of a superabsorbent gel involves the search for a compromise between its absorption properties and strength.

In modern superabsorbent materials, this compromise is achieved by forming a strong shell with a sufficiently high density of crosslinks on the surface of slightly crosslinked polymer granules [40]. However, this modification may somewhat decrease the ability of the gel to swell. Sometimes the mechanical properties are improved by introducing a certain proportion of covalently bound rigid chains (e.g., in the form of a crosslinking agent [41–43]) into the polymer network. The reinforcing rigid chains may also be tightly held in the gel even without forming covalent bonds [44]. This is possible provided that the rigid chains are capable of aggregating with each other to form large aggregates with dimensions exceeding the gel mesh size. Pinching of a part of the network chains in the aggregates leads to effective immobilization of the rigid-chain polymer in the gel and a considerable increase in the elastic modulus [44].

An alternative way to improve the mechanical properties of a polymer gel and retain its good absorption capacity consists in forming a composite gel structure comprising a rigid framework embedded into a flexible-chain network. Such gels were obtained, for example, by acrylamide polymerization in aqueous suspensions of a finely dispersed crystalline mineral (sodium montmorillonite) [45, 46]. In the course of polymerization in this system, the polyacrylamide gel is incorporated immediately into the mineral platelets, which accounts for the formation of a sufficiently strong composite structure with good mechanical characteristics [45].

## SOME APPLICATIONS OF STRONGLY SWELLING POLYMER GELS

One of the main fields of application for superabsorbent gels is the fabrication of various hygienic materials and articles for the absorption of physiological liquids (diapers, etc.) [47]. This field consumes several hundred tons of polymers for hydrogels per year [39].

Another important application field is agriculture, where superabsorbent gels are used as a means of retaining ground water in drought-prone regions [39]. This problem is extensively studied in Egypt [48] in attempts to increase fertility of the desert soils. The application of superabsorbent gels in this field is based on their ability to swell in the soil pores and retain water, preventing both rapid evaporation and infiltration into deep underground layers. The plants may absorb water both from closed pores and from the swollen gel: the osmotic apparatus in most cultivated plants is capable of extracting most of the water stored in hydrogels [49]. Possessing this property, hydrogels can also be used as a base of nutritional media for plant growing by hydroponics.

The superabsorbent gels are successfully applied in civil engineering. The related water-absorbing materials are employed for coating the concrete blocks used in the construction of tunnels. As soon as water permeates the structure walls, the superabsorbent gel swells to tightly fill the gaps between the blocks and prevent water from penetrating into the tunnel. This method is widely employed in the construction of tunnels for railroads and highways in Japan, and it was successfully used for constructing the Channel tunnel [48]. The superabsorbent gels enter into the composition of polymeric ribbons used for protecting underground cables in optical communication lines [50].

Superabsorbent gels are employed for the production of a special laminated material comprising two paper sheets separated by a thin layer of a superabsorbent gel powder. This laminated material is used, for example, for packing fresh meat and poultry products. The gel absorbs excess liquid; at the same time it prevents the stored product from overdrying [51]. Superabsorbent gels form the base of synthetic coating materials capable of substituting for snow; these materials are used, for example, in Japan where the first sport hall with artificial snow hills (50 m wide and 120 m long)

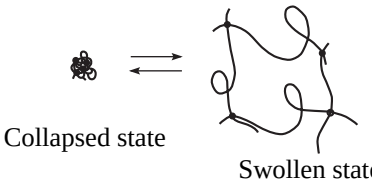


**Fig. 5.** Schematic diagram illustrating two states of a polymer gel: collapsed (subchains in a globular conformation) and swollen (subchains in a coiled conformation) [51].

was opened in 1991. The artificial snow is composed of gel granules swollen in water and frozen. The frozen gel granules retain their properties at a temperature of up to +15°C (in contrast to finely crushed natural ice that can serve only up to +5°C) [52]. Specialists consider the possibility of using superabsorbent gels as a means of strengthening soils, offering protection against slides and sels [48]. It was also suggested [48] that wallpaper based on a nonwoven material filled with superabsorbent gel powder can maintain a preset level of humidity in a room.

Thus, polyelectrolyte gels are highly valuable superabsorbent materials that can be employed in various fields. The area of application will significantly expand when strong composites of superabsorbent gels with nonwoven materials, rubbers, etc. are created [48].

## GEL COLLAPSE

If repulsive forces dominate in the interactions between polymer chain units in the gel network, the gel exhibits strong swelling and behaves as a superabsorbent. Should the attractive forces contribute (in addition to the repulsive forces) to the interaction between network units, the gel may exhibit a collapse.

The phenomenon of collapse consists in the gel volume strongly decreasing (by a factor of several tens or hundreds) in response to a rather small change in the external factors such as temperature, pH, various additives (thermodynamically poor solvent, surfactant, linear polymer), light, electric field, etc. The gel volume variations during collapse are reversible and, in macroscopic samples, visually observable.

A driving force for the transition from swollen to collapsed state is the violation of the balance between attractive and repulsive interactions in the gel under the action of external factors. The most effective repulsive interactions are related to the long-range electrostatic forces (the main one of which is the osmotic pressure of counterions). The van der Waals forces, hydrophobic contacts, hydrogen bonds, and attractive forces between oppositely charged ions contribute to the attractive interactions that may give rise to gel collapse.

The collapse belongs to phenomena that were first predicted theoretically and only later observed in experiment. The possibility of collapse in gels was originally predicted in 1968 by Dusek and Patterson [53]. They pointed out that the volume of a gel sample may exhibit a jumplike change upon application of external pressure to the sample. Using the Flory–Huggins equation of state, it was demonstrated that the presence of an external force may lead to the appearance of a Maxwell loop on the gel isobar. A similar phenomenon in a single polymer chain in solution, known as the coil–globule transition, was theoretically studied by Ptitsyn and Eizner [54], de Gennes [55], and Lifshitz *et al.* [56]. It was suggested that gel collapse is essentially a macroscopic manifestation of the coil–globule transition in the network subchains. This process can be considered as a first-order phase transition [53, 57, 58] between two phases differing in their subchain conformations and concentration of the crosslinked polymer, one phase representing the swollen gel and the other—the same gel in the collapsed state (Fig. 5).

It was not until 1978 (i.e., ten years after the first prediction) that the collapse was experimentally observed by Tanaka [59], who studied the swelling of slightly crosslinked polyacrylamide gels in water–acetone mixtures (water being a thermodynamically good solvent and acetone—a precipitant) and established that adding a certain amount of acetone led to a jumplike decrease in the volume of water-swollen gel.

There was one interesting point in this experiment: numerous attempts (including those of Tanaka) at reproducing the effect were unsuccessful. The results confirmed that the gel exhibited contraction, but the transition from swollen to collapsed state was continuous rather than jumplike as in the first experiment Tanaka reported in [59]. Only after a few months of experimental work was it established that the character of the transition (discrete versus continuous) depends on the gel prehistory—the conservation time interval from polymerization to the beginning of gel washing from residues of the polymerization mixture. An increase in the conservation time to a certain value leads to the phenomenon of discrete collapse.

Figure 6 illustrates the collapse in polyacrylamide gel observed in water–acetone mixtures of various compositions. The gel samples swollen in water exhibit contraction when acetone is added to the external solution. As is seen, the contraction in freshly prepared samples has a continuous character. As the time of conservation of the gel samples increases, the acetone concentration inducing the collapse tends to grow and a change in the gel volume upon collapse increases. For a gel sample stored over 60 days, the sample volume upon collapse drops by a factor of about 500 [26].

Tanaka [26] suggested that the phenomenon of "aging" during the conservation time interval is related to charging of the gel network chains. Later, Ilavsky *et al.* [60] showed that the charges appear as a result of the partial hydrolysis of amide groups. Indeed, potentiometric titration [61] of a linear polyacrylamide formed

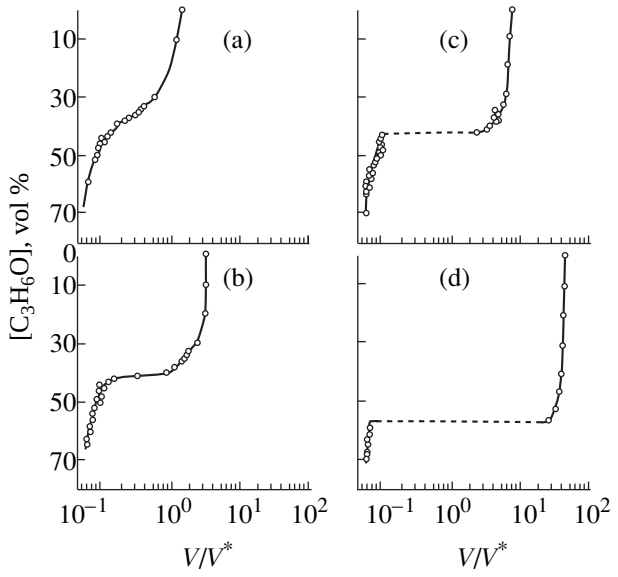


**Fig. 6.** Collapse in polyacrylamide gels swollen in water–acetone mixtures and observed after gel conservation for various times: (a) 0 (initial gel); (b) 2 days; (c) 6 days; (d) 60 days. $V/V^*$ is the swollen to initial gel volume ratio; $[C_3H_6O]$ is the acetone concentration.

under similar conditions showed that about 1% of the chain units occur in a charged state. Thus, it was suggested that the character of the collapse is significantly affected by the presence of even a small fraction of charged units in the network chains [26].

This hypothesis was experimentally confirmed by the results observed on specially synthesized gels with charged network chains. It was demonstrated that the higher the fraction of charged groups, (i) the greater the gel volume change upon collapse, (ii) the higher the concentration of thermodynamically poor solvent inducing the collapse, (iii) and the more pronounced the collapse is (Fig. 7). In order to explain these facts, it is necessary to take into account the osmotic pressure of mobile counterions in charged gels [26]. This factor accounts for the strong gel swelling in a thermodynamically good solvent (water). On the other hand, the collapsed gel phase (formed as a result of the attraction between uncharged monomer units in a poor solvent) is less affected by the motion of counterions, because this phase is stabilized by non-Coulomb interactions between the chain units (the region of stability for this phase must decrease with increasing fraction of charged chains in the gel network).

Thus, the difference in volume between the swollen and collapsed phase in charged gels may reach three orders of magnitude. A transition between these highly different gel states (strongly swollen or collapsed) separated by a high potential barrier may proceed only in a jumplike manner. Moreover, a transition of the charged gel from strongly swollen into collapsed state would require a greater amount of the precipitant (compared to that required for the transition in the uncharged gel) to be added in order to ensure that the non-Coulomb attraction of uncharged units would exceed the osmotic pressure (repulsion) of counterions. This circumstance explains a shift of the collapse toward greater concentrations of the thermodynamically poor solvent with increasing content of charged units in the gel (Fig. 7).

The phenomenon of collapse was studied in a large number of synthetic polymer gels, including polyan-

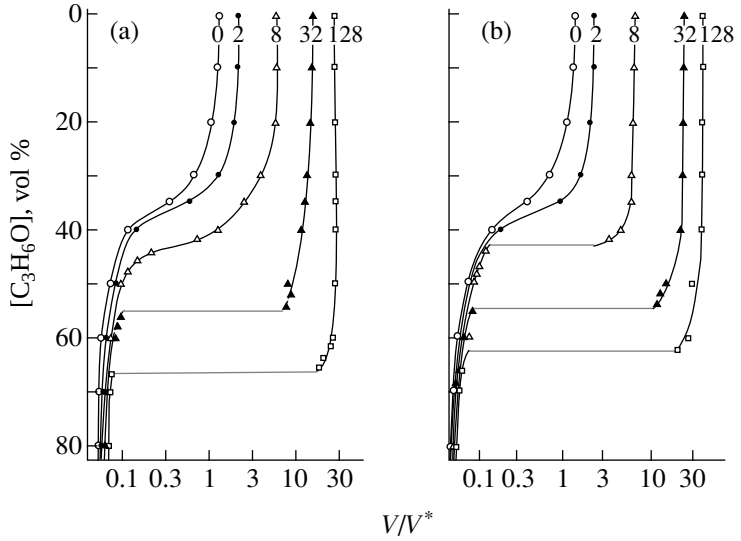


**Fig. 7.** Collapse in (a) positively and (b) negatively charged polyacrylamide gels with different contents of charged units (indicated by figures at the curves, mmol/l) swollen in water–acetone mixtures: (a) methacrylamidopropyltrimethylammonium chloride gel; (b) sodium acrylate gel. Total monomer concentration, 700 mmol/l [62]. $V/V^*$ is the swollen to initial gel volume ratio.

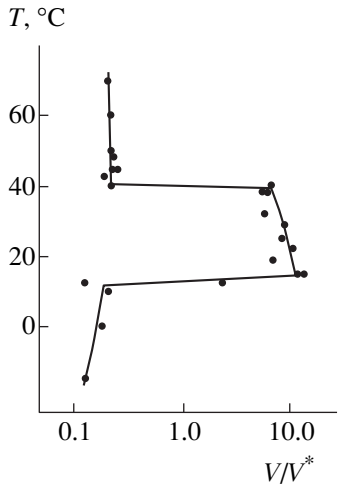


**Fig. 8.** The temperature-induced swelling and collapse in the cationic gel of an acrylamide–trimethyl-(*N*-acryloyl-3-aminopropyl)ammonium iodide copolymer in a 40% aqueous acetone solution [74]. *V*/*V** is the swollen to initial gel volume ratio.

ionic [26, 59, 62–73], polycationic [62, 72, 74–77], polyampholytic [72, 78–91], and neutral [70, 82–95]. It was demonstrated that the collapse can be observed in natural polymer gels as well. There are three main groups of the natural polymer : proteins, polysaccharides, and nucleic acids. Amiya *et al.* [96] prepared and studied covalently crosslinked gels of gelatin (protein), agarose (polysaccharide), and DNA. The results showed that the gels of all three types exhibit collapse on a decrease in the quality of solvent (water–acetone mixture). Thus, the phenomenon of collapse can be observed in any polymer gels of both synthetic and natural origin [7, 51, 96].

Recently, Verdugo *et al.* [51, 97] presented a convincing example to demonstrate the phase transition in a polymer gel occurring in the biological world. As is known, slugs contain mucin in an extremely compact form. Once secreted into the external medium, mucin absorbs water and swells to increase in volume by a factor exceeding 1000. In this way, slugs are capable of storing water and maintaining the humid medium necessary for their survival. For a long time, it was unclear to biologists how slugs could store mucin in a compact form in their bodies full of water. Verdugo *et al.* [51, 97] established that mucin exhibits collapse on adding calcium ions and suggested that this secretion is stored in the slug's body in a collapsed state due to a high concentration of calcium ions. A similar mechanism for maintaining a humid medium is apparently employed by some other animals (e.g., eels). It was suggested that analogous mechanisms are inherent in mucins lining the internal walls of the gastrointestinal tract in the human organism [51].

Thus, the phase transitions in polymer gels represent a universal phenomenon. These effects were observed in all the gels studied (irrespective of their nature and chemical structure) and are widely occurring in nature.

## RESPONSIVE GELS

When in the vicinity of the collapse transition, polymer gels may change their volume in a very sharp and reversible manner in response to very small variations in the properties of the medium (temperature, pH, solvent composition, etc.) capable of inducing the collapse. Owing to this possibility, these polymeric systems are called responsive gels. Sometimes they are also referred to as smart or intelligent materials; these terms reflect their ability to follow in a preset (programmed) way some small changes in the medium [98].

Sensitivity of the polymer gels with respect to a change in one or another external factor is determined by the chemical composition, namely, by the presence of atomic groups affected by this factor. Depending on the factor inducing the phase transition, responsive gels can be divided into several major groups sensitive to temperature (thermosensitive gels), solvent composition, pH, ions, light (photosensitive gels), electric field, biochemical factors, etc.

### *Thermosensitive Gels*

The thermosensitive gels can be subdivided into three groups [74, 88, 99], depending on whether an increase in temperature leads to swelling, collapse, or combined (so-called convexo) behavior. Different responses of the gel to temperature are determined by the nature of interactions involved in the phase transition. If the collapse is due to the van der Waals forces or hydrogen bonds, the hydrogel exhibits an increase in the degree of swelling with temperature, since heating decreases both the van der Waals attraction and the strength of hydrogen bonds. On the contrary, the gels featuring the collapse related to hydrophobic interactions exhibit contraction on heating because an increase in the temperature favors stronger hydrophobic attraction.

Heating a gel in which the collapse is determined by an interplay of interactions of several types may be accompanied by phase transitions of both types–swelling and collapse [88, 100]. Here, increasing temperature may induce sequential (phase reversal) transformations of the collapse–swelling–collapse and swelling–collapse–swelling types. The former sequence was observed, for example, in the anionic gel of acrylamide–sodium vinylsulfonate copolymer swollen in a 65% aqueous acetone solution [100] and in the cationic gels of acrylamide–trimethyl-(*N*-acryloyl-3- aminopropyl)ammonium iodide copolymer swollen in a 40% aqueous acetone solution (Fig. 8) [74]. The latter sequence was reported for the uncharged gels based on some *N*-(alkoxyalkyl)acrylamides swollen in water. As

the temperature increases, these gels first collapse (at 25–30°C) and then swell (at 40–45°C) [101].

A volume-phase transition in a thermosensitive gel was originally observed by Tanaka *et al.* [83] in a poly(*N*-isopropylacrylamide) (PNIPA) gel swollen in water. At present, this gel is one of the most thoroughly studied thermosensitive polymer systems. The PNIPA gel occurs in a swollen state in water at room temperature, but exhibits collapse on heating to 33°C [83]. This effect is explained by a temperature-induced increase in the hydrophobic interactions between nonpolar groups in the polymer. This is accompanied by release of the water molecules structurized at the surface of these groups, which results in an increase in the total entropy of the system. It was demonstrated [102] that dehydration of a single monomer unit in PNIPA is accompanied by liberation of 13 water molecules. A number of other polymer gels exhibiting collapse on heating were reported later [7, 88], representing for the most part gels based on poly(*N*-alkylacrylamides) [7, 103], as well as poly(vinyl methyl ether) [87, 93, 95, 104] and poly(*N*-vinyl caprolactam) [105].

Since it is known that hydrophobic interactions are the main driving force for gel collapse with increasing temperature, the behavior of thermosensitive gels can be controlled by varying the ratio of hydrophobic and hydrophilic units in the polymer chain. Based on the results of investigations, it is possible to synthesize gels with any preset temperature of the phase transition. The study of a series of poly(*N*-alkylacrylamide) gels with various alkyl substituents, showed that the gels with hydrophobic groups possessing a greater area in contact with water exhibit collapse at a lower temperature [88, 103]. Using various *N*-alkyl-substituted polyacrylamides, Hirasa *et al.* [87] obtained various thermosensitive hydrogels with phase transition temperatures ranging from 19.8°C for poly(*N*-methyl-*N*-propylacrylamide) to 72.0°C for poly(*N*-ethylacrylamide).

The phase transition temperature in neutral thermosensitive gels can be controlled by adding small fractions of charged units [106, 107]. The greater the fraction of charged units in the gel, the more pronounced the shift in the phase transition temperature [108, 109]. Adding charged units not only affects the temperature but changes the character of the phase transition as well: the transition becomes sharper and increases in amplitude (Fig. 9). For a sufficiently large content of the charged units, the gel may lose temperature sensitivity because the hydrophobic attraction will no longer overcome the electrostatic repulsion.

### *Gels Sensitive to Solvent Composition*

For almost any gel, we may select a poor solvent whose additives may induce the gel to collapse. The classical example of polyacrylamide gel collapsing in a water–acetone mixture was considered in detail above.

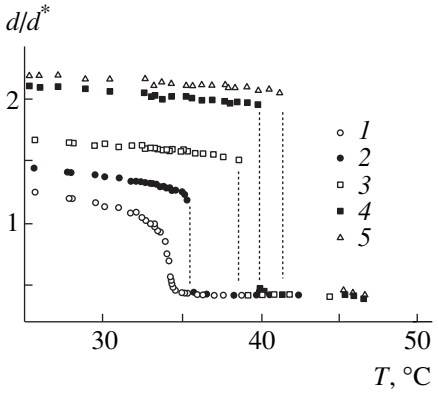


**Fig. 9.** The pattern of temperature-induced collapse in poly(*N*-isopropylacrylamide) (PNIPA) gels with variable content of charged sodium acrylate units: (*1*) 0; (*2*) 8; (*3*) 32; (*4*) 50; (*5*) 70 mmol/l [109] (*d*/*d** is the ratio of gel diameters in the swelled and initial state).

In these gels, the point of collapse can be shifted by adding small amounts of charged units (Fig. 7).

It should be borne in mind that components of a mixed solvent may be nonuniformly distributed between gel and solution. For a swollen gel, the composition of the mixed solvent inside the gel usually coincides with that of the external solution, whereas the collapsed gel is enriched with the thermodynamically good solvent component as compared to the external solution [110]. The results of a theoretical analysis [110] showed that such a redistribution of the solvent components between collapsed gel and solution is more pronounced in a system with a greater value of the parameter of interaction $\chi_{AB}$ between the solvent components. This is related to the fact that an increase in the $\chi_{AB}$ value reflects the growing tendency to phase separation in the solvent, whereby preferential solvation of the thermodynamically good solvent component in the network becomes energetically favorable (leading to the free energy variation in the same direction as that upon the phase separation).

A number of gels were reported that featured two phase transitions in the course of gradual change of the composition of a mixture of two solvents (the relative content of each component varied from 0 to 100%). Figure 10 shows the variation of the degree of swelling of a PNIPA gel in a water–DMSO mixture of variable composition [83, 92]. Both water and DMSO taken separately are thermodynamically good solvents for PNIPA, in which the polymer gel is in the swollen state. However, adding water to a gel swollen in DMSO (or vice versa) results in gel collapse. Under similar conditions, a polyacrylamide gel does not undergo any phase transitions at all (Fig. 10).

Reentrant phase transitions of the same type (swelling–collapse–swelling) were also observed in a weakly charged gel based on a NIPA–sodium acrylate copolymer swollen in a water–methanol mixture [70] and in

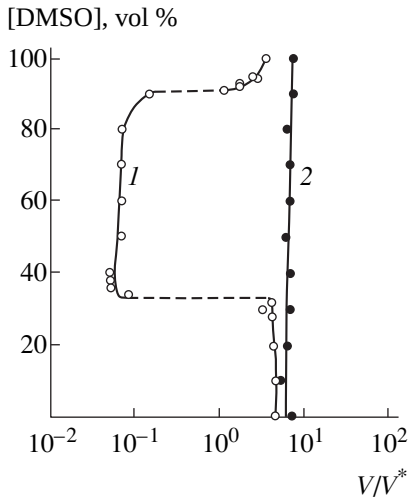


**Fig. 10.** Variation of the swelling ratio of (*1*) PNIPA and (*2*) polyacrylamide gels in the DMSO–water solvent mixture of variable composition [83]; $V/V^*$ is the swollen to initial gel volume ratio.

an *N*,*N*-diethylacrylamide–sodium acrylate copolymer swollen in a water–DMSO mixture [68]. These phase transitions are related to the fact that interactions between the molecules of both solvent components produce a greater gain in the free energy than do interactions between each solvent and the network monomer units. As a result, the network undergoes a collapse that decreases the area of the polymer in contact with solvent. These experimental data are in complete agreement with the results of theoretical analysis of polymer network collapse in a two-component solvent [110].

It should be noted that the theory [110] predicts the possibility of reentrant phase transitions of both swelling–collapse–swelling (described above) and collapse–swelling–collapse types in mixed solvents. The latter situation takes place if a network is swollen in a mixture of two solvents, each of them being thermodynamically poor for the polymer. Then the network is in a collapsed state in each solvent taken separately, while being capable of swelling in their mixture.

Under certain conditions, we may observe a double reentrant transition. For example, a weakly charged gel based on NIPA–sodium acrylate copolymer swollen in a water–methanol mixture [70] doubly undergoes the reentrant phase transition when the ethanol concentration is gradually increased. This behavior is fully consistent with predictions of the theory [110] and is explained by redistribution of the solvent components between gel and solution, whereby leveling of the solvent compositions inside and outside the gel at equal volume fractions of both solvent components is caused by a gain in the entropy of mixing.

### *pH-Sensitive Gels*

Sensitivity with respect to pH is observed in gels containing weak acid or weak base groups capable of ionizing in response to pH variations. The uncharged gels occur in the collapsed state, while ionization leads to gel swelling caused by the osmotic pressure of mobile counterions. The hydrogels containing acid groups exhibit swelling in an alkaline medium but collapse in an acid solution, where ionization is suppressed. In contrast, the hydrogels with base groups swell in an acid medium and collapse on increasing pH (Fig. 11).

Polyampholytic gels swell on acidification or alkalization of the medium, while occurring in the most contracted state in the intermediate pH range (Fig. 11) corresponding to an equimolar ratio of positively and negatively charged units (isoelectric point) [80, 111]. Gel contraction at the isoelectric point is related both to a decrease in the osmotic pressure of counterions and to the Coulomb attraction of oppositely charged network units.

By simultaneously introducing thermosensitive monomer units and a small fraction of units with groups capable of pH-induced ionization, we may obtain a gel combining the properties of pH and temperature sensitivity. Such gels were synthesized, for example, using the NIPA–sodium acrylate copolymers (negatively charging gel) [106] and the NIPA copolymers with 2-dimethylaminoethylmethacrylate [106]

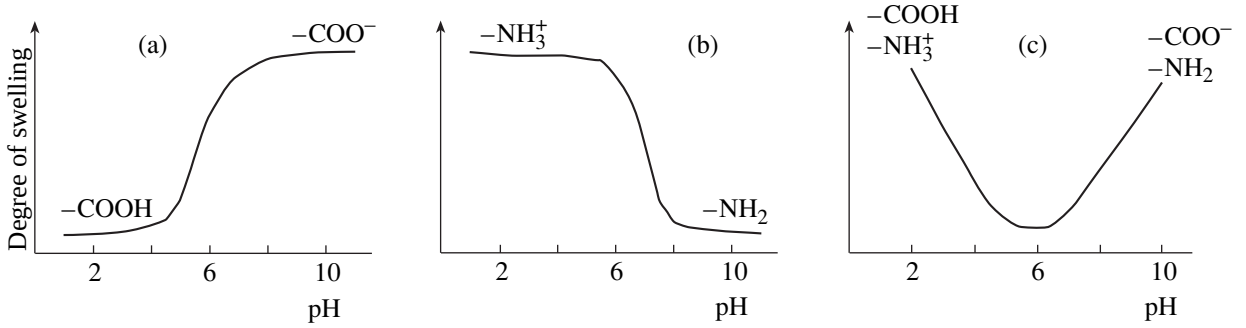


**Fig. 11.** Schematic diagrams illustrating the possible effects of pH on the swelling of gels containing network units of (a) weak acid, (b) weak base, and (c) both acid and base types (polyampholytic gel).

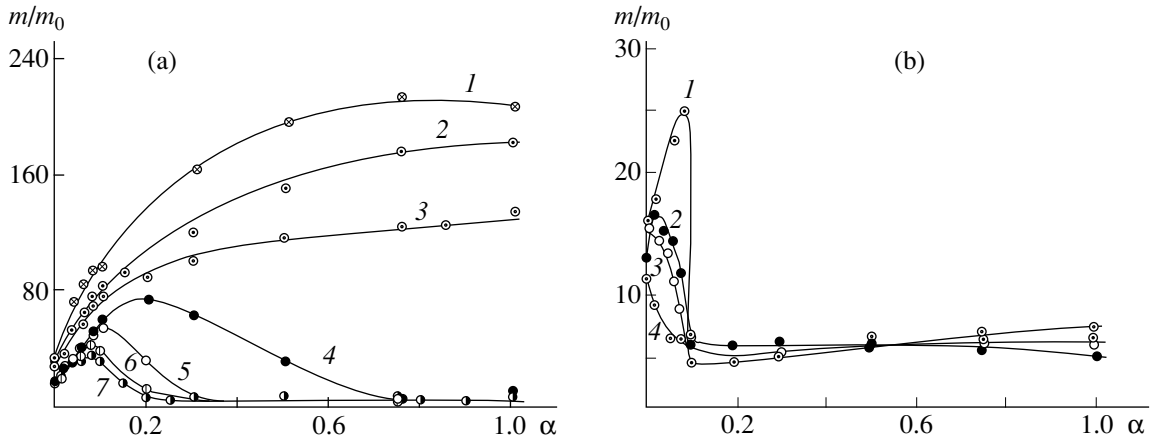


**Fig. 12.** Plots of the degree of swelling vs. degree of ionization for a PMAA gel in various solvents: (a) methanol–water mixtures containing (*1*) 0, (*2*) 20, (*3*) 50, (*4*) 65, (*5*) 80, (*6*) 90, and (*7*) 95 vol % of methanol; (b) methanol–dioxane mixtures containing (*1*) 90, (*2*) 75, (*3*) 65, and (*4*) 20 vol.% of methanol [113]. ($m/m_0$ is the swollen to initial gel mass ratio).

and diethylaminoethylmethacrylate [112] (positively charging gels).

It is interesting to note that the situation of ionization-induced swelling is not the only one possible. Figure 12 shows a series of plots of the degree of swelling versus degree of ionization for a PMAA gel in various solvents [113]. As is seen, there are three main types of gel behavior on ionization. The first regime, in which the gel swells with increasing charge, is observed in a polar medium (polyelectrolyte regime). The second regime, when the gel collapses upon charging, takes place in a low-polarity medium (ionomer regime). The third regime characterized by the passage from swelling to collapse with increasing degree of ionization is observed for an intermediate solvent polarity (mixed polyelectrolyte–ionomer regime).

The different character of variation of the degree of swelling in the course of ionization in these regimes is explained by different states of counterions in the gel. When the counterions formed due to the ionization are free (polar medium), the gel exhibits swelling due to their osmotic pressure (polyelectrolyte regime). In the low-polarity medium, the counterions are not free but condense at the oppositely charged chain units to form ion pairs (Fig. 3). These ion pairs tend to aggregate with the formation of multiplets acting as additional crosslinks in the gel, which causes gel collapse in the ionomer regime. The gel immersed in a medium of intermediate polarity contains both free ions and ion pairs. The initial swelling at low degrees of ionization is related to a growth in the osmotic pressure of free counterions with increasing network charge. The collapse transition is observed when the concentration of ion pairs becomes sufficient for the formation of multiplets. In this state, the equilibrium between free ions and ion pairs shifts toward the latter and the gel collapses. The collapse is caused both by a decrease in the osmotic pressure of mobile counterions and by the additional network crosslinking related to ion pair aggregation into multiplets (mixed polyelectrolyte–ionomer regime). Thus, ionization of the gel may lead to either collapse or swelling, depending on the polarity of the medium [113].

### *Ion-Sensitive Gels*

Adding low-molecular-mass salts may significantly affect the swelling behavior of polymer gels, mostly of the polyelectrolyte type, by screening the network charge.

Let us first consider the polyelectrolyte gels in which the network units possess charges of the same sign. Here, the salt effect depends on the thermodynamic quality of a solvent into which the gel is immersed. In the case of a thermodynamically good solvent, adding a monovalent salt usually leads to gradual contraction of the gel, while the same salt added to a relatively poor solvent may induce a jumplike collapse (Fig. 13) [65]. The salt effect is manifested when the additive concentration becomes comparable with the concentration of free counterions (determining the osmotic pressure) inside the gel [114]. The gel contraction is related primarily to a decrease in the osmotic pressure difference inside and outside the gel. In addition, establishing the Donnan equilibrium results in that the low-molecular-mass salt concentration inside the polyelectrolyte gel is always lower than that outside [115]. In contrast to the case of swollen gels, introducing salts into a system with a collapsed gel does not affect the gel state.

Gel contraction or collapse upon adding a multivalent salt is usually observed at a markedly lower additive concentration than that necessary for a monovalent salt (Fig. 13) [65, 116, 117]. The difference is explained

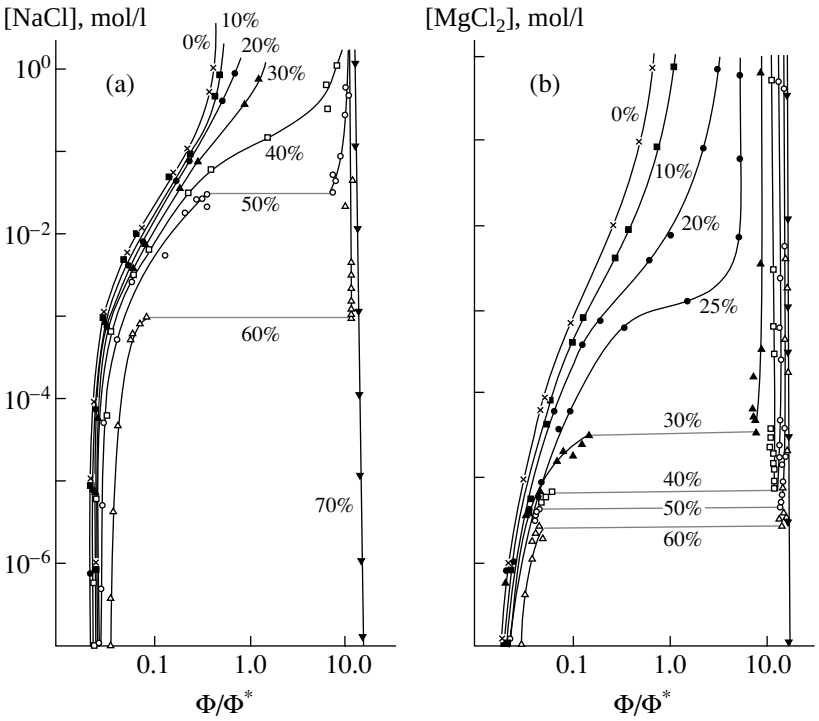


**Fig. 13.** Effect of the low-molecular-mass salts (a) NaCl and (b) $MgCl_2$ on the swelling behavior of acrylamide–sodium acrylate copolymer gels in water–acetone mixtures of various compositions (acetone concentrations in vol.% indicated at the curves) [65]; $\Phi/\Phi^*$ is the final to initial polymer volume fraction ratio.

by several factors. First, by a decrease in the total number of counterions inside the network, which are necessary to compensate for the network charging. Second, by the multivalent ions being attracted stronger than monovalent ones to the oppositely charged groups in the network (this decreases the mobility of counterions and, hence, their ability to produce osmotic pressure). Third, by the polyvalent ions electrostatically binding simultaneously to several gel network units, which is equivalent to the formation of additional crosslinks in the network. The greater the multivalent ion charge, the lower the salt concentration necessary to induce the gel transition to the collapsed state.

A qualitatively different pattern is observed on adding low-molecular-mass salts to the polyampholytic gels. Here, establishing the Donnan equilibrium results in that the salt concentration inside the gel is higher than that outside. Inside the gel, the salt shields attraction of the oppositely charged network units, thus favoring swelling of the gel [115].

Irie [89] synthesized gels possessing selective sensitivity with respect to certain ions. For this purpose, special groups selectively interacting with the given ion were introduced into the polymer gel. For example, a gel sensitive to potassium ions was obtained by immobilizing a benzo-18-crown-6 in a PNIPA gel (Fig. 14) [89]. The size of the ring cavity in this crown ether molecule is just suited to accommodating the potassium ion. This accounts for the tight binding of potassium ions to crown ether by means of the ion–dipole interactions between potassium cations and electronegative oxygen atoms of the ring.

This gel, occurring in a contracted state at the collapse threshold, exhibits abrupt swelling upon the appearance of potassium ions in solution. This is explained by the fact that the gel converts from uncharged to polyelectrolyte upon binding $K^+$ ions to crown ether fragments. The potassium ions sorbed by the gel attract an equivalent amount of counterions, which enter the gel and produce the exerting osmotic pressure leading to gel swelling. No such effect was observed for the salts of other alkali metals (lithium and sodium) that did not bind to the crown ether employed [89].

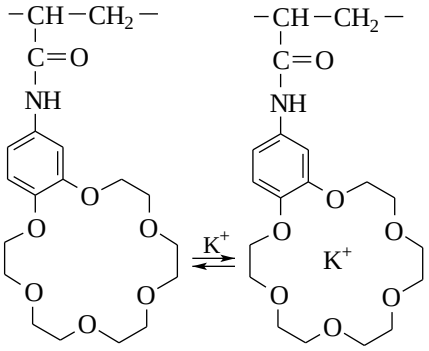


**Fig. 14.** A schematic diagram illustrating potassium ion binding to a crown ether.

### *Photosensitive Gels*

Light-sensitive gels were synthesized [85, 118, 119] using a copolymer of NIPA with photosensitive molecules of bis(4-(dimethylamino)phenyl)(4'-vinylphenyl)methyl leukocyanide capable of dissociating under UV irradiation [118]. The action of light on this gel is based on the photoionization effect. In the absence of the UV light, a PNIPA gel containing 1% of these photosensitive groups exhibits a phase transition to the collapsed state at 30.0°C. Upon exposure of the sample to UV radiation, this temperature increases to 32.6°C due to ionization of the photosensitive groups (Fig. 15). In a gel maintained at a constant temperature in the interval between 30.0 and 32.6°C, for example at 31.0°C, the UV irradiation produces a reversible jumplike transition from collapsed to swollen state [118]. The effect was explained by the osmotic pressure of cyanide ions appearing as a result of the UV-induced photoionization of the sample. As soon as the UV irradiation is switched off, the charged groups vanish and the gel passes back to the collapsed state.

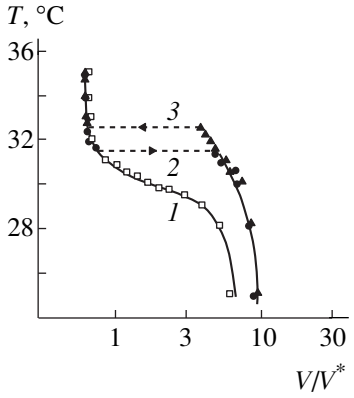


**Fig. 15.** Effect of temperature on the swelling of a NIPA copolymer with photosensitive molecules of bis(4-(dimethylamino)phenyl)(4'-vinylphenyl)methyl leukocyanide capable of dissociating under UV irradiation [118]: (*1*) heating and cooling in the absence of UV radiation; (*2*) cooling under UV irradiation; (*3*) heating under UV irradiation. *V*/*V** is the swollen to initial gel volume ratio.

Suzuki and Tanaka [85] also reported on the synthesis of gels sensitive to visible light. The structure of these samples consists of a PNIPA network with covalently bound molecules of a chromophore (Cu-chlorophyllin). The gel, occurring initially in a swollen state at a temperature close to that of the phase transition (31.5°C), collapses under illumination at a radiant power exceeding 85 mW. It was suggested that the light induces a local temperature increase inside the gel due to absorption and thermal dissipation of the light energy by the chromophore molecules.

### *Gels Sensitive to Electric Field*

Charge transfer under the action of an applied electric field may induce a change in the degree of swelling in ion-containing gels. Consider a strip of a weakly charged anionic gel. Upon electric field application, both polyions and small counterions in the gel are subject to electric forces acting in opposite directions depending on the charge sign. Since the negative charges are fixed in the polymer network, the electric field predominantly transfers the counterions (cations) moving toward the cathode. As a result, the concentration of mobile ions producing the osmotic pressure near the cathode markedly increases, leading to gel swelling in this region. In contrast, the gel at the other electrode (anode) shrinks and the whole sample strip exhibits bending [66, 120, 121].

Similar manipulations with a gel in a sufficiently poor solvent (in the vicinity of a collapse threshold) can lead to the collapse induced by the electric field [66]. This process is reversible and the gel exhibits swelling when the electric field is switched off.

Gels sensitive to electric field were also obtained using the process of reversible complex formation between a polyelectrolyte gel and an oppositely charged surfactant [122]. In this system, the surfactant ions transferred by the electric field concentrate at one of the electrodes to form complexes with oppositely charged gel network units. The complex formation is accompanied by surfactant ion aggregation to micelles, which results in gel contraction at the site of complexation. This eventually leads to bending of the gel plate. On changing the polarity of the electrodes, the absorbed surfactant molecules desorb, while new surfactant molecules concentrate at the opposite electrode and form complexes with the gel. Thus, the polymer gel plate can be driven to repeated bending and straightening by alternating the electrode polarity [122].

### *Biochemically Sensitive Gels*

Special investigations were devoted to the synthesis of gels exhibiting phase transitions in the presence of certain biopolymer molecules [7, 20–22, 51, 108, 123–125]. This task is solved using special interactions of various types, such as antigen–antibody, ligand–receptor, etc. Molecules of a biochemically active substance (e.g., an enzyme or a receptor) are immobilized in a gel occurring in the state close to the collapse threshold. The target molecules falling within the gel interact with the active substance, thus breaking the equilibrium and leading to gel swelling or collapse.

Kokufuta *et al.* [125] used a PNIPA gel to immobilize an enzyme (concanavalin A) possessing specific binding sites for polysaccharides. On binding a charged polysaccharide (dextran sulfate), the gel swells due to the osmotic pressure of ions. Replacing the dextran sulfate by an uncharged polysaccharide (α-methyl-*D*-mannopyranoside) causes the gel to collapse.

## SOME APPLICATIONS OF RESPONSIVE GELS

The ability of hydrogels to react in a sharp and reversible manner in response to changes in the external conditions determines their use as functional materials in various fields. Below we will mention only some of these applications

### *Membranes with Controlled Permeability*

There are two principal mechanisms determining the passage of substances through polymeric membranes [107]: (i) diffusion in the polymer matrix and (ii) diffusion through pores. In the former case, a substance dissolves in the membrane material and diffuses in the polymer medium. In the latter case, the membrane is considered as a sieve comprising a system of interpenetrating channels and pores, through which the molecules diffuse without interacting with the polymer. In hydrogels, the second mechanism is usually dominating. This implies that the lower the degree of gel swelling, the smaller the membrane permeability [22]. A collapse of the gel completely blocks diffusion through the polymeric membrane [22]. In membranes fabricated from responsive gels, we may change the permeability in a reversible manner by varying the hydrogel swelling with the aid of some controlled external parameter (e.g., temperature) [21, 22].

If a gel exhibits collapse on heating (thermosensitive gels based on PNIPA or poly-*N*-acryloylpyrrolidine), the permeability of the gel decreases with increasing temperature [21, 22]. The permeability of temperature-insensitive gels (e.g., poly-2-hydroxyethylmethacrylate gel) increases on heating, which is related [21] to the diffusion rate of dissolved substances increasing with temperature. Using this approach, Bae *et al.* [21] obtained membranes, the permeability of which increases or decreases with temperature (depending on the gel composition employed).

### *Catalysts with Controlled Activity*

The ability of gels to collapse can be used for creating reversible catalysts using catalyst molecules immobilized in the gel network. The action of such catalysts can be readily halted by inducing collapse of the gel and then restored by allowing the gel to swell again. The catalytic process termination is related to a sharp decrease in the gel permeability with respect to the reagents, whereby the catalyst becomes inaccessible. As the gel swells, the diffusion process is restored and the reaction proceeds further.

Polymer gels capable of collapsing under "mild" conditions (in aqueous media at temperatures not exceeding 40–45°C and neutral pH values) can be used for preparing reversible biocatalysts with the active components represented by enzymes [108, 123, 126, 127]. Such a reversibly swelling biocatalyst acquires the advantages of immobilized enzymes (whereby the enzyme becomes more stable and can be readily separated from the reaction mixture and repeatedly used). However, this system may possess certain disadvantages related primarily to diffusion hindrances to the substrate permeation inside the gel and the removal of reaction products to the external solution (even in the swollen gel). These disadvantages can be eliminated using the characteristic ability of responsive gels to change their volume depending on the external factors. An interesting method for solving the task was proposed by Park and Hoffman [123, 128, 129]. The idea is to create a microscopic pump exhibiting swelling and contracting cycles to absorb a liquid in the gel pores (on swelling) or drive it back to the surrounding solution (on shrinking), thus markedly enhancing the mass transfer. For this purpose, the authors used a thermosensitive gel in which the swelling and contraction cycles were induced by small periodic temperature variations in the vicinity of the collapse threshold [123, 128, 129].

### *Carriers for Controlled Drug Release*

Polymer matrices have been used for a long time to develop new medicinal forms. Polymeric carriers ensure prolonged drug action by allowing the parent compound to release slowly from a matrix to the organism. However, a polymer matrix can not only control the rate of drug release, but may provide for drug delivery to a target site in the organism that has to be treated [22].

Systems for the targeted delivery of drugs are designed taking into account the fact that the gastrointestinal tract of humans contains compartments with markedly different pH levels. For example, the stomach contains an acid medium (pH 1.4) while that in the intestine is close to neutral (pH 6.7–7.4). For this reason, the drug carriers are frequently based on the pH-sensitive gels [130]. When such a gel carrying a drug enters the organism, the drug is released at the site where the conditions favor gel swelling.

**pH-Sensitive weak-base gels.** Polymer gels containing weak base groups collapse in neutral or alkaline media (Fig. 11) and swell in an acid medium (e.g., in the stomach). Therefore, these gels can be used for the targeted transport of drugs to the stomach. Owing to the fact that these gels collapse at a neutral pH value typical of the oral cavity, they can also be used for making shells protecting drugs against dissolution in saliva and protecting patients against the bitter taste of many drugs (taste-masking application) [131]. In particular, special gels for these applications were developed based on a copolymer of methyl methacrylate and *N*,*N*-dimethylaminoethylmethacrylate (a weak base capable of charging in acid media).

**pH-Sensitive weak-acid gels.** Polymer gels containing weak base groups collapse in acid media and swell in an alkaline medium (Fig. 11). Therefore, carriers based on these gels retain a parent drug inside the

gel in the stomach (at pH 1.4), thus acting as protective shell [130]. Upon reaching the intestine (pH 6.7–7.4), the gel swells and releases the drug.

These preparations are especially important for the treatment of disorders such as pancreatitis. Patients with pancreatitis must permanently receive enzymes with meals, otherwise the products are not properly digested and absorbed in the small intestine. At present, pancreatitis is usually treated with drug preparations based on the enzyme amylase. However, pharmacological investigations showed that only a small fraction (<10%) of the drug administered by a patient reaches the intestine in the active state. The reason for the drug activity loss is enzyme inactivation by a low-pH medium in the stomach. The weak-acid hydrogels are of no less importance for administration of the anti-inflammatory drug indomethacin, but here the task is to protect the stomach against the undesired drug action (indomethacin produces strong irritation of the stomach tissues and may even lead to their perforation [107]), rather than to shield the drug from the aggressive medium of stomach. The gel matrix completely blocks the release of indomethacin in the stomach.

It was suggested that a shell for peroral drugs to protect them in the stomach can be formed by hydrogels synthesized through copolymerization of NIPA, acrylic acid, and a polydimethylsiloxane (PDMS) macromonomer with vinyl terminal groups [107, 130]. These copolymers are sensitive with respect to both pH (due to the acrylic acid units) and temperature (due to the NIPA units). In addition, the hydrogels contain hydrophobic PDMS domains that may serve as a depot for storing hydrophobic drugs.

Thus, the pH-sensitive hydrogels not only play the role of a matrix ensuring controlled drug release at a definite site of the organism, but perform an additional protective function as a shell for peroral drugs.

Pathological processes taking place in the organism usually involve variations in pH, temperature, and the concentrations of certain substances. Taking this into account, it is possible to create drug release systems with feedback, whereby a given pathological process initiates the drug release. The creation of such a self-controlled drug preparation—an artificial pancreas representing a device capable of secreting insulin in response to a change in the glucose concentration—may help in meeting serious problems of patients suffering from diabetes mellitus. Certain success in solving this task was achieved with the aid of hydrogels. As a rule, the glucose sensors are based on the enzyme glucose oxidase. The enzyme is immobilized in a pH-sensitive weak-base gel containing a saturated insulin solution. Glucose diffusing from the external solution into the hydrogel is oxidized by glucose oxidase to gluconic acid. Formed in the course of the reaction, this acid produces ionization of the pH-sensitive gel and, hence, its swelling. The gel swelling favors the outdiffusion of insulin from gel to external solution. Thus, the system provides for the controlled release of insulin in response to the glucose content in the external solution [128, 132–134].

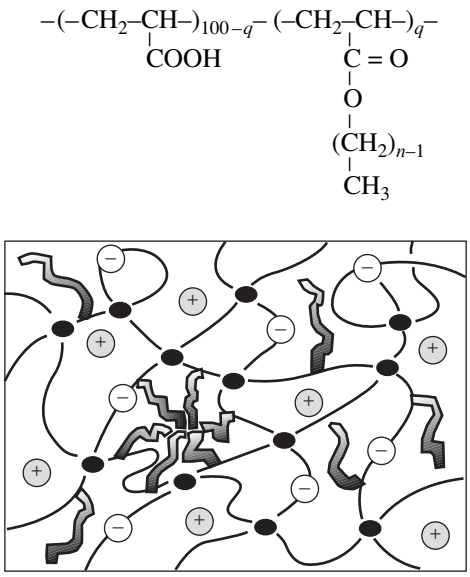


**Fig. 16.** The chemical formula and schematic diagram of the structure of a poly(acrylic acid) gel modified by hydrophobic groups. The hydrophobic groups covalently bound to the network chains are capable of interacting with one another to form micelle-like aggregates.

For further progress in this field, it is necessary to develop methods for the synthesis of pH-sensitive hydrogels with different pH of transition from collapsed to swollen state. This would allow us to select with greater precision the site and rate of drug release. A possible way of solving this task was proposed in [36, 77]. According to this approach, a small number of units with nonpolar *n*-alkyl side groups are introduced into a weak-acid or weak-base polymer gel. A typical structure of the resulting system is schematically depicted in Fig. 16. When the gel is not charged, the hydrophobic attraction of *n*-alkyl groups leads to the formation of micelle-like aggregates stabilizing the collapsed state. Acting as additional effective crosslinks in the gel structure, these hydrophobic aggregates hinder the network swelling triggered by ionization induced by pH variations [36]. Thus, the transition to swelling in this gel requires a greater change in pH (i.e., a greater number of charged units) such that the electrostatic repulsion forces would be sufficient to destroy the aggregates. By varying the content of units with hydrophobic groups or the length of the side *n*-alkyl chain, it is possible to change in a controlled manner the threshold pH level corresponding to the gel transition from collapsed to swollen state (Fig. 17) [36]. In addition, the hydrophobic aggregates formed by the nonpolar groups in a collapsed gel may serve as "reservoirs" for nonpolar drugs. As the degree

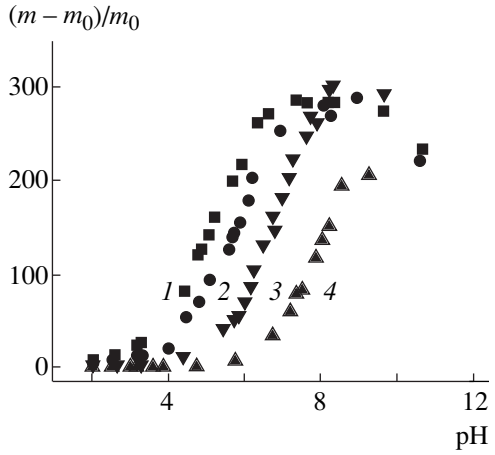


**Fig. 17.** Plots of the degree of swelling vs. equilibrium pH of the external solution for the gels of (*1*) unmodified (*2*–*4*) modified poly(acrylic acid) containing (*2*) 2.5, (*3*) 10, and (*4*) 20% of *n*-octylacrylate units [36]. ($m$ and $m_0$ are the masses of swollen and dry gel, respectively.)

of network ionization increases, the hydrophobic aggregates are destroyed and the drug is released from the gel.

### *Soft Manipulators*

All living organisms move due to the isothermal conversion of chemical energy into mechanical work, which is expressed, for example, by the contractions of muscles or the motions of cilia in microorganisms [135]. These systems can be modeled by hydrogels based on "responsive" polymers capable of strongly swelling (expanding) or contracting in response to external stimuli in the form of thermal, chemical, or electric energy. The history of creating the first systems of this type dates back to the 1950s and is related to the names of Kuhn and Katchalsky—well known authorities in polymer chemistry [136, 137].

At present, works on the development of various devices employing the ability of hydrogels to change their volume and/or shape in response to the action of external factors are in progress; the most extensive investigations are being performed in Japan [11, 120, 138, 139]. In particular, Kurauchi *et al.* [120] used a polyelectrolyte gel deformed by an electric field to construct a "soft" manipulator, consisting of a robot arm with soft gel fingers, which was capable of carefully taking and transferring an egg without damaging it. Another device had the form of an artificial fish with a soft gel tail, the motion of which was controlled by an electric field [120] so that the fish was able to swim.

A disadvantage of gels as materials for manipulators is their relatively slow response to external actions: the rate of this response is frequently determined by the network reaction rate (depending on the rate of diffusion processes in the network) rather than by the rate of change of the external stimulus itself. As is known, the time necessary to reach the equilibrium gel swelling or collapse is proportional to the square of the characteristic gel size [1], reaching several days for macroscopic samples with dimensions on the order of ~1 cm. In order to accelerate the gel response to the external action, it is possible to use small-size gel elements (thin films or balls). For a spherical gel with a diameter on the order of a few microns, the time of response to external actions is measured in milliseconds.

However, a more promising approach consists in using alternative external factors, the response to which does not depend on the diffusion process inside the network. A possible method was proposed by Zrinyi *et al.* [140–144], according to which magnetite ($Fe_3O_4$) nanoparticles possessing pronounced ferromagnetic properties are introduced into the gel structure. The response time of such a gel upon a change in the applied magnetic field is very fast (~1 s) and independent of the gel size. The "magnetic" gels are capable of performing complicated motions in response to a computer-controlled magnetic field [142].

The gel manipulators controlled by such external actions exhibit soft, flexible, and noiseless operations. Constructing gel-based soft manipulators is a rapidly developing direction of polymer network technology, which has good prospects for creating robots with human-like motions [122].

## MICROSTRUCTURE OF RESPONSIVE GELS

The competition between opposing attractive and repulsive forces may not only change the macroscopic properties of a gel (collapse versus swelling), but favor self-organization of the network units in the gel volume as well, with the formation of regular microstructures of various types.

Let us consider a weakly charged polyelectrolyte gel occurring in an aqueous medium in a state close to the collapse threshold. The gel is subject to two competitive forces: repulsive (related primarily to the translational entropy of counterions) and attractive (caused by non-Coulomb interactions). The translational entropy of counterions tends to retain the gel in the swollen state. At the same time, a decrease in the thermodynamic quality of the solvent would enhance the non-Coulomb attraction of monomer units to each other, leading eventually to a collapse.

In weakly charged polyelectrolyte gels obeying the condition of macroscopic electroneutrality, the transition to a collapsed state is made unfavorable because of a considerable decrease in the entropy of counterions. However, the energy gain due to a short-range interaction of the network chain units can also be realized in the swollen state by forming a microphase-separated structure with alternating aggregates of hydrophobic uncharged units and strongly swollen regions accommodating most of the charged units and counterions (Fig. 18). In this microphase-separated structure, the

counterions do not lose their translational entropy: they are still capable of traveling over the whole swollen gel volume, while the number of unfavorable contacts between uncharged units and water is markedly decreased (Fig. 18). The phenomenon of microphase separation in polyelectrolyte gels swollen in aqueous media was experimentally observed in 1991–1992 independently by two groups of researchers headed by Prof. Candau in France [145, 146] and by Prof.

Shibayama in Japan [71]. Shibayama *et al.* [71, 147] studied the microstructure of weakly charged polyelectrolyte gels based on NIPA–sodium acrylate copolymers in heavy water by the method of small-angle neutron scattering (SANS). The PNIPA gels are thermosensitive gels exhibiting collapse on heating. The main factors responsible for the collapse are the hydrophobic interactions, which increase with temperature. The SANS curve showed a peak (Fig. 19) that appeared at 40°C and grew with further increase in the temperature. The presence of a peak in the SANS curve at a finite value of the wavevector $\mathbf{q}_0$ is indicative of the formation of a microphase-separated structure with a characteristic spatial period of $\lambda = 4\pi/\mathbf{q}_0$. It should be emphasized that this structure appears at 40°C, when the gel is still in a strongly swollen state (a discrete collapse in this gel is observed at 50.8°C).

Similar results were obtained by Schosseler *et al.* [145, 146, 148–150] for weakly charged gels of polyacrylic and polymethacrylic acids swollen in heavy water.

The SANS data were interpreted using a theory developed by Borue and Erukhimovich for microphase separation in a linear polyelectrolyte solution in a thermodynamically poor solvent [151, 152]. It was demonstrated [71] that both the shape of the experimental SANS curve and the peak position coincide with those predicted by the theory (Fig. 19). The spatial fluctuation period determined from the experimental data [71] was also close to the theoretical value [152].

The formation of microstructures (microphase separation) in polymer gels may be caused by various factors. The appearance of microstructures in the gels in aqueous media considered above was explained by the competition of electrostatic and hydrophobic interactions, the former factor (predominantly the osmotic pressure of counterions) being responsible for the repulsion between network chain units. Later, microstructure formation was observed in systems where the electrostatic factor accounted for the attraction of chain units and non-Coulomb interactions stabilized the swollen gel state. These microstructures form under the conditions favoring strong Coulomb interactions between ions, for example, in low-polarity media or in systems with large ion charge. The attraction between counterions and charged chain units in the gel leads to the formation of ion pairs, followed by their aggregation into multiplets as a result of the dipole–dipole attraction (Fig. 3).

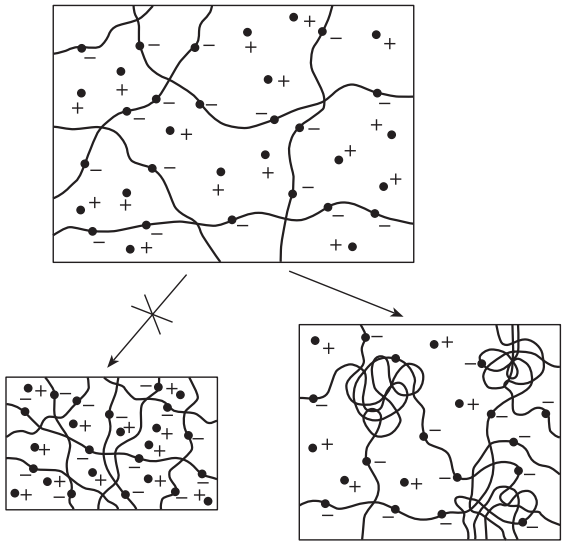

**Fig. 18.** Schematic diagrams illustrating the possibility of microphase separation in a weakly charged polyelectrolyte gel swollen in a thermodynamically poor solvent.

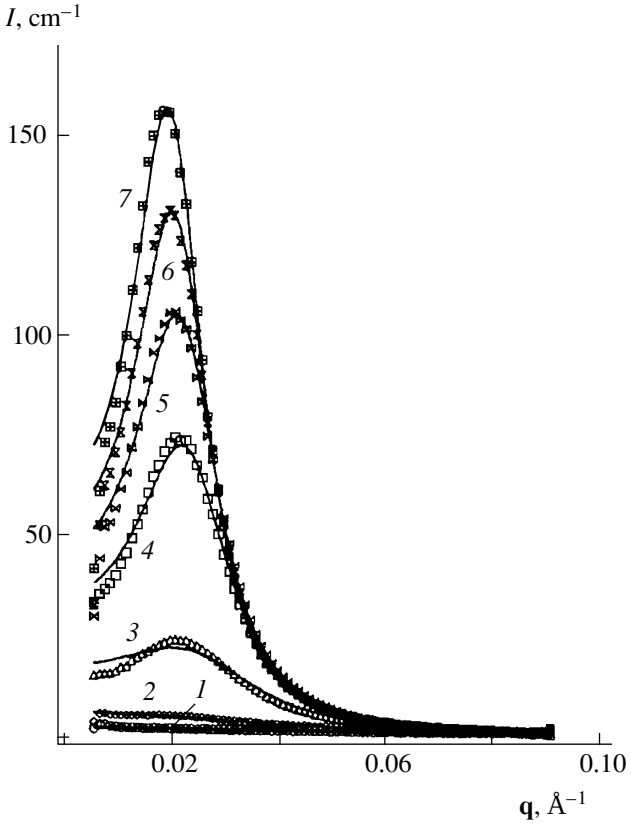


**Fig. 19.** Plots of the SANS intensity vs. wavevector (symbols) for a NIPA–sodium acrylate copolymer gel (95 : 5, mol %) swelled in heavy water at various temperatures $T$ = 32 (*1*); 36 (*2*); 40 (*3*); 44 (*4*), 46 (*5*); 48 (*6*); 50°C (*7*) [71]. Solid curves show the theoretical neutron scattering curves calculated using the Borue–Erukhimovich theory [151, 152].

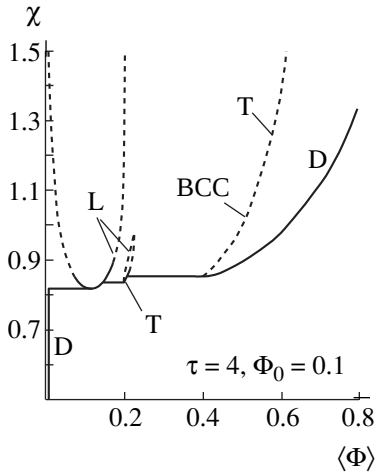


**Fig. 20.** A plot of the average volume fraction of polymer in the gel ⟨Φ⟩ versus the polymer–solvent incompatibility parameter χ calculated for a polyelectrolyte gel (fraction of charged units, 0.06; number of monomer units in subchains between crosslinks, 1000; τ = 4; volume fraction of polymer in the gel, 0.1) [156]. Solid curve represents the equilibrium collapse curve; dashed lines indicate metastable states featuring microdomain structures of various morphologies (L = lamellar; T = triangular; D = disordered; BCC = body-centered cubic).

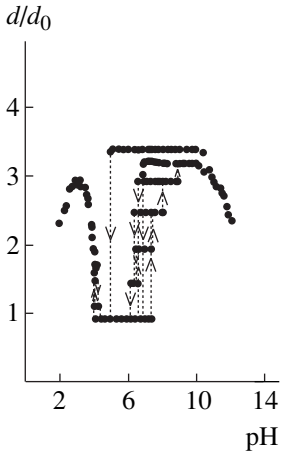


**Fig. 21.** The pattern of room-temperature (25°C) phase transitions induced by pH variations in a gel based on a copolymer of acrylic acid (460 mmol) and methacrylamidopropyltrimethylammonium chloride (240 mmol) [25]. ($d/d^*$ is the ratio of gel diameters in the swelled and initial state.)

The formation of multiplets in gels was reported for the first time in [153–155]. The objects of investigation were gels of polyacrylate and polymethacrylate of europium. Since counterions in these gels were capable of producing fluorescence, the ion aggregates were studied by the fluorescent spectroscopy technique. It was established that charged groups are nonuniformly distributed over the gel volume, being concentrated in aggregates (multiplets) including on average about seven counterions (with the corresponding oppositely charged groups of chain units). Similar to the hydrophobic aggregates in PNIPA gels, the ion aggregates (multiplets) begin to form when the gel is still in the swollen state (and are retained in the gel upon collapse). Thus, the formation of microstructures in polymer gels can be observed near the collapse threshold in the systems featuring competition between the tendency to aggregation on the short-range scale and the tendency to long-range stabilization counteracting gel collapse.

Proceeding from the analogy with microphase separation in block copolymers, it could be expected that the resulting microstructures may possess various morphologies—and this assumption was confirmed in [156]. Moreover, we may expect that the transitions between microstructures with different morphologies can be controlled by varying external parameters (temperature, pH, etc.). This assumption is corroborated by the results of theoretical calculations for the collapse in weakly charged polyelectrolyte gels in a thermodynamically poor solvent with allowance for possible microstructure formation [157].

Figure 20 shows a theoretical plot of the average volume fraction of polymer in the gel ⟨Φ⟩ (this quantity is inversely proportional to the gel volume $V$) versus the polymer–solvent incompatibility parameter χ. As seen from this diagram, the pattern of gel contraction in this case (in contrast to the classical case) exhibits several stages. As the solvent quality decreases, the gel undergoes a transition from a disordered swollen phase to an intermediate phase with lamellar microdomains; this is followed by the next jumplike change in the gel volume accompanied by the transition of microdomains from lamellar to hexagonal structure comprising cylindrical hydrophobic micelles; finally, the last jumplike change in the gel volume gives rise to a collapsed disordered phase. A characteristic period of the microdomain structure formed in the intermediate stages of nontrivial morphology variation in all cases amounts to tens of nanometers. As seen from Fig. 20, the collapse region may feature a number of metastable phases (in addition to those mentioned above); therefore, nonmonotonic variation of the parameter χ may be accompanied by hysteresis phenomena.

Thus, according to the theoretical analysis [157], the possible existence of microdomains of stable phases with various morphologies in a collapsing polyelectrolyte gel may render the collapse a multistage process involving the formation of microphase-separated nanostructures in the intermediate stages. These theoretical results may provide an explanation for the recent experimental data [51, 79, 94, 158, 159] indicating the existence of several intermediate phases in collapsing gels. The multiple phases were originally observed by Annaka *et al.* [79, 158, 159] in a gel based on a copolymer of cationic and anionic monomers (capable of forming hydrogen bonds with one another in the

uncharged state). It was found that a change in the pH or temperature of an aqueous medium is accompanied by jumplike transitions in the gel between several phases differing in their volumes (Fig. 21). The number of phases and transitions depends on the ratio of cationic to anionic monomer units in the gel network. Intermediate phases were also observed in some other gels [51, 94], but their structures were not characterized.

## CONCLUSIONS

Thus, the behavior of swollen polymer gels has proved to be richer and more complicated than one might think. These objects offer wide possibilities for controlled variation of both their macroscopic state and microscopic structure. Evidently, a key point in the possibility of controlled action upon polymer gels is the knowledge of the principal forces responsible for their behavior.

In recent years, slightly crosslinked polymer gels have found increasing practical applications. Their use is based on two main properties: the capacity for strong swelling and the ability to sharply change their volume in response to small variations in the external conditions. In this review, we have briefly considered the main physical factors determining the properties of polymer gels and indicated some promising applications of these systems.

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